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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

doctet@nutter.com

Office Action Summary

Application No.

10/766,642

Applicant(s)

ATALA ET AL.

Examiner

ALLISON M. FORD

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 04 January 2010.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-4, 6-10, 12, 16, 23, 28, 29 and 33-43 is/are pending in the application.
- 4a) Of the above claim(s) 7, 38, 39 and 42 is/are withdrawn from consideration.
- 5) ☒ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-4, 6, 8-10, 12, 16, 23, 28, 29, 33-37, 40, 41 and 43 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-940)
- 3) ☐ Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date _____
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date _____
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: _____

DETAILED ACTION

Applicants' response of 1/4/2010 has been received and entered into the application file. Claims 1, 6, 7, 10, 23 and 33-37 have been amended. New claims 38-43 have been added.

However claim 7, as currently amended, and new claims 38, 39 and 42 require use of a species of cell in the claimed methods which is patentably distinct from the other species of cells which are currently under examination. Specifically, claim 7, as currently amended, and new claims 38, 39 and 42 define the first or second cell population as *endothelial progenitor cells*; this species of cell has not previously been presented for examination. Endothelial progenitor cells are independent or distinct from vascular endothelial cells and myoblasts (the previously examined species of cell types) because endothelial progenitor cells have different differentiation potentials than either vascular endothelial cells or myoblasts, are derived from distinct sources than vascular endothelial cells or myoblasts, and have different utilities as far as organ augmentation. In addition, none of the species of cell types are obvious variants of each other based on the current record.

Since applicant has received an action on the merits for the originally presented invention (which includes myoblasts and vascular endothelial cells as the specified cell types), the species of vascular endothelial cells and myoblasts have been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 7, 38, 39 and 42 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Claims 1-4, 6-10, 12, 23-16, 28-29 and 33-43 are pending in the current application, of which 1-4, 6, 8-10, 12, 23-16, 28-29 and 33-37, 40, 41 and 43 have been considered on the merits.

Response to Arguments/Amendments

Applicants' arguments submitted on 1/4/2010 have been fully considered. The grounds of rejection have been significantly modified due to the amendments; however, the arguments will be briefly answered, in so far as they are relevant to the instant rejections.

Applicants traverse the rejections based on Naughton et al on the grounds that Naughton et al fail to teach or suggest each of the limitations of the instant claims, specifically that Naughton et al fail to teach or suggest utilizing two populations of cells with distinct functions, wherein the first population of cells is transiently transfected and a second population of cells to be assimilated at the target site.

Applicants have also asserted that Naughton et al 'teaches away' from use of genetically engineered cells transfected to express angiogenesis modulating agents (citing ¶0006 of Naughton et al), and thus one would not have been motivated to modify the method of Naughton et al to utilize genetically engineered cells, such as is required by the current invention.

Applicants further assert the secondary and tertiary references fail to remedy these deficiencies and/or the Examiner has relied on impermissible hindsight, using the instant application as a 'template' to piece together the teachings of the prior art to arrive at the instant application.

Applicants' arguments have been fully considered, but are not found persuasive.

In response to Applicants' argument that Naughton et al does not teach or suggest utilizing two populations of cells with distinct functions, Applicants are respectfully pointed to ¶0025, 0028, 0034 and 0038 of Naughton et al, where they specifically disclose the stromal tissue may comprise stromal cells with or without additional cells; the embodiment wherein the stromal tissue comprises stromal cells with additional cells is the basis for the rejection. It is further respectfully submitted that neither independent claims requires the first and second cell populations to have distinct functions.

In response to Applicants' argument that Naughton et al does not teach or suggest transiently transfecting the first population of cells, it is acknowledged that Naughton et al does not disclose *transiently* transfecting the cells with a plasmid encoding VEGF, however, it is maintained that Naughton et al does specifically teach use of *transfected* cells engineered to express VEGF (See Naughton et al, ¶0046-0054). Penn et al is relied upon to render obvious the use of *transiently transfected* cells which have been transfected with a plasmid encoding VEGF. Penn et al further disclose there is a clear benefit to using *transiently* transfected cells, specifically that transient expression of VEGF is sufficient to induce angiogenesis, but does not cause the systemic effects or hemangioma formation associated with long-term expression of VEGF (See Penn et al, ¶0004 & 0099-0102). Thus it is respectfully submitted that the motivation to substitute *transiently transfected* cells expressing VEGF for those which appear to constitutively express VEGF in the method of Naughton et al is found in the prior art, Applicant's application was not relied upon as a 'template' for this modification.

In response to Applicants' argument that Naughton et al does not disclose the second population of cells to be assimilated at the target site, it is respectfully submitted that, as the rejection now stands, the stromal cells are being considered 'the second cell population' and Naughton et al does clearly intend for the stromal cells to assimilate into the existing tissue. For example, Naughton et al teaches that the stromal tissue construct can be attached to the target tissue site by natural cellular adherence (See Naughton et al, ¶0058 & 0067); natural cellular attachment means the cells of the stromal tissue construct have assimilated into the existing tissue to form an adherence.

In response to Applicants' argument that Naughton et al 'teach away' from use of cells genetically modified to express angiogenesis factors, it is respectfully submitted that the discussion of hurdles encountered in the prior art does not serve to effectively 'teach away' from what is specifically suggested within the same reference. At ¶0006 Naughton et al references the work of Losordo et al, where retroviral vectors encoding for VEGF were injected directly into heart tissue (Losordo et al actually report

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their naked DNA injection resulted in improved cardiac function (See Losordo et al, abstract)); thus the technique of Losordo et al is not a cell based gene therapy, but direct gene therapy using retroviral vectors. The method of Penn et al utilizes cell based gene therapy, wherein the cells are transfected with a plasmid encoding for the angiogenesis modulating agent, thus the problems associated with direct injection of retroviral vectors are not relevant. Furthermore, the fact that Naughton et al go on to state that technical hurdles exist in the art with regards to gene-therapy methods does not preclude one of ordinary skill in the art from attempting such gene therapy methods, rather it simply suggests that the techniques are difficult, and require skill. Thus Applicants' argument of Naughton et al 'teaching away' is not found persuasive.

In response to Applicants' argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). With regards to use of transiently transfected cells (as taught by Penn et al), it has been discussed above that Penn et al does provide explicit motivation to use transiently expression of VEGF, as opposed to long-term express. Otherwise the current rejections of record have been modified so as to particularly point out the rationale and/or motivation to make the pro-offered modifications, so as to be clear hindsight reconstruction was not relied upon.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 29 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 29 is rejected as lacking antecedent basis for the limitation "the encapsulated first population of cells" in the second line of the claim. Claim 23, from which claim 29 depends, no longer requires encapsulation of the first cell population.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claim 1-4, 6, 8, 9, 12, 23, 25, 26, 28, 40, 41 and 43 are rejected under 35 U.S.C. 103(a) as being obvious over Badylak et al (US 2003/0216811), in light of Badylak et al (Biomaterials, 1999), and in view of Penn et al (US 2004/0161412 A1).

Badylak et al disclose submucosa tissue-derived grafts and methods of using said grafts to repair damaged or diseased tissues. Specifically, the tissue graft comprises a vertebrate intestinal submucosa tissue seeded with endothelial cells and at least one additional exogenous cell population (See Badylak et al, ¶0016). Badylak et al report their method is particularly effective in promoting vascularization at the target tissue site (See Badylak et al, ¶0022).

The endothelial cells can be any type of endothelial cell, including vascular endothelial cells (See Badylak et al, ¶0017).

The at least one additional exogenous cell population may be selected from fibroblasts, smooth muscle cells, skeletal muscle cells, cardiac muscle cells, multi-potential progenitor cells, pericytes, osteogenic cells, or any other suitable cell type (See Badylak et al, ¶0018). The at least one additional exogenous cell population may be selected based on the type of tissue to be repaired, i.e. the at least one additional exogenous cell population may be selected to be a tissue-specific cell type; cardiac muscle cells are specifically disclosed for instances where cardiac tissue is to be repaired (See Badylak et al, ¶0019).

Badylak et al disclose the intestinal submucosa may be in an injectable fluidized or gel form (See Badylak et al, ¶0005 & 0033).

In use, the submucosa-tissue derived graft is seeded with the population of endothelial cells and the at least one additional exogenous cell population *in vitro*; cultured *in vitro* for a time sufficient to induce formation of vessels or vessel-like structures; and then injected into a vertebrate at the site in need of repair (See Badylak et al, c.g., ¶0049).

The method of Badylak et al is comparable to the method of the instant claims as follows:

The intestinal submucosa is considered to appropriately read on a matrix material which may form an organ construct. Intestinal submucosa comprises collagen type I (See Badylak et al, Biomaterials, Pg. 2257, 2nd full paragraph); collagen is a naturally occurring polymer, thus the submucosa comprises a polymer.

In the injectable form the intestinal submucosa is considered to appropriately read on an injectable polymer matrix that comprises collagen type I (as recited in claims 1, 8 and 9); the injectable form further reads on the matrix material of claims 23 and 26 and may be considered a hydrogel (claim 25).

For the purposes of this rejection either of the vascular endothelial cells or the at least one additional exogenous cell population may be considered the first or the second cell population, as both

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cell populations are intended to be assimilated into the target tissue region. Thus, the step of co-culturing the vascular endothelial cells and the at least one additional exogenous cell population is comparable to the claimed step of "selecting a second population of cells to be assimilated at a target tissue region upon implantation" (claim 1) as well as the step of "culturing at least a second population of cells on a matrix material to produce an organ construct" (claim 23).

Finally, the step of injecting the cell-seeded tissue graft into a target tissue region is considered to read on the claimed step of "injecting the first population of cells and the second population of cells and the polymer matrix into the target tissue region" (claim 1) as well as the step of "implanting the organ construct and the first population of cells *in vivo* at a target site to replace or augment organ function" (claim 23). Both the endothelial cells and the at least one additional exogenous cell population assimilate into the target tissue region, thereby augmenting organ function.

The method of Badylak et al differs from the claimed method in that Badylak et al does not disclose a step of transiently transfecting the first population of cells (which may be either cell population) with a plasmid encoding an angiogenesis modulating agent, specifically VEGF, so that, upon injection the first population of cells will express the angiogenesis modulating agent (VEGF).

However, at the time the invention was made it was well known in the art that cells intended for transplantation for organ augmentation may be genetically engineered to express one or more growth factors which will promote cell survival and angiogenesis; this technique is known as cell-based gene therapy (See, e.g. Penn et al ¶0009 & 0067-0072).

Penn et al teach implantation of skeletal myoblasts which have been transfected with VEGF into ischemic myocardium in order to restore function to the ischemic cardiac tissue (See Penn et al ¶ 0067-0070). The transfection may be achieved by vector-based plasmid DNA transfection (See Penn et al,

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¶0092 & ¶0100-0102)). Furthermore, Penn et al state that the myoblasts cells which transiently express VEGF are useful to stimulate cell differentiation and regenerate ischemia damaged tissue (See Penn et al, ¶0020 & ¶0044-0045). Penn et al teach that local and transient expression of VEGF is sufficient to induce neovascularization, while minimizing systemic effects and hemangioma formation (See Penn et al, ¶0004 & 0099-0102).

With regards to the length of time the VEGF is produced, Penn et al teach that the duration of the transient expression is a result effective variable that would be routinely optimized by one of ordinary skill in the art (See Penn et al, pg. 8, paragraphs 0099-0102). Penn et al teach that the cells can be transiently transfected so as to express a therapeutic amount of VEGF; Penn et al further teaches that it is well within the scope of one skilled in the art to determine the appropriate therapeutic amount on an individual basis, as factors such as size, age, sex, presence of other drugs, and concentration of the active drug, all effect the optimal duration of expression. Therefore, the duration of the transient expression of VEGF would have been routinely optimized by one of ordinary skill in the art at the time the invention was made, especially with lack of evidence supporting the claimed time period is critical (relevant to claim 2).

It is submitted that, based on the teachings of Badylak et al and Penn et al, one of ordinary skill in the art would have found it *prima facie* obvious to utilize the transiently transfected myoblasts of Penn et al as the 'at least one additional exogenous cell population' in the graft of Badylak et al, and to then apply the graft, containing vascular endothelial cells and transiently transfected myoblasts, to ischemic myocardium in order to induce growth and development of blood vessels in the ischemic tissue, thereby improving cardiac function. One would have been motivated to combine the prior art elements in order to produce an improved treatment option for ischemic myocardium, as prior art methods had varying degrees of success. Particular motivation is based on the fact that treatment for myocardial ischemia

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involves angiogenesis and vasculogenesis of the ischemic tissue (See Penn et al, ¶0004); Badylak et al state their tissue graft is particularly effective at inducing vascularization (See Badylak et al, ¶0022); Penn et al state the myoblasts form new cardiac muscle tissue (See Penn et al, ¶0070), and the VEGF is an angiogenic promoting agent that increases vascular density (See Penn et al, ¶0044).

One would have had a reasonable expectation of successfully employing the transiently transfected myoblasts of Penn et al as the 'at least one additional exogenous cell type' because Badylak et al disclose skeletal muscle cells as one type of cell which may be provided as the tissue specific at least one additional exogenous population of cells (See Badylak et al, ¶0018-0019). Myoblasts are progenitor muscle cells, thus skeletal myoblasts may be considered a species of skeletal muscle cell.

Thus it is submitted that it would have been *prima facie* obvious to one having ordinary skill in the art to modify the method of Badylak et al so as to utilize the myoblasts of Penn et al, which are transiently transfected with a plasmid encoding VEGF, as the 'at least one additional exogenous cell population' in the tissue graft of Badylak et al. In this manner the transiently transfected myoblasts may be considered 'the first cell population', and the vascular endothelial cells may be considered 'the second cell population'. The graft may be injected into ischemic myocardium where the myoblasts will necessarily express the VEGF thereby supporting cell survival and assimilation and differentiation of both the myoblasts and endothelial cells into the myocardial tissue to improve cardiac function. Thus the modified method of Badylak et al reads on the method of instant claims 1, 2, 12, 23 and 41. Please note that myoblasts (the first cell population) are also considered to read on undifferentiated cells (claim 3).

Alternatively, it would have been within the purview of one skilled in the art to transiently transfect the *vascular endothelial cells* with a plasmid encoding VEGF (per the method of Penn et al) and to seed the transiently transfected vascular endothelial cells with normal myoblasts onto the injectable

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submucosa matrix of Badylak et al. It is not critical which cell type expresses the VEGF, but rather only that at least one cell type which is provided to the target tissue is capable of expressing the VEGF in order to increase the concentration of VEGF at the target site. Penn et al disclose that the transfection method is applicable to any cell type (See Penn et al, ¶0069), thus one would have had a reasonable expectation of successfully transiently transfecting the vascular endothelial cells as opposed to the myoblasts. In this manner, the transiently transfected *vascular endothelial cells* may be considered 'the first cell population', and the myoblasts may be considered 'the second cell population.' The graft may be injected into ischemic myocardium where the vascular endothelial cells will necessarily express the VEGF thereby supporting cell survival and assimilation and differentiation of both the myoblasts and endothelial cells into the myocardial tissue to improve cardiac function. Thus the modified method of Badylak et al reads on the method of instant claims 1, 2, 4, 6, 23, 40 and 43.

Therefore the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Claim 1-4, 6, 8, 9, 10, 12, 23, 25, 26, 28, 33-37, 40, 41 and 43 are rejected under 35 U.S.C. 103(a) as being obvious over Badylak et al (US 2003/0216811), in light of Badylak et al (Biomaterials, 1999), and in view of Penn et al (US 2004/0161412 A1), and further in view of Stewart et al (US 2006/0251630 A1).

The teachings of Badylak et al and Penn et al are set forth in detail above. Briefly, Badylak et al disclose a method for repairing damaged or diseased tissue comprising:

- providing a fluidized intestinal submucosa material as a matrix;
- co-culturing vascular endothelial cells and at least one additional, tissue-specific exogenous cell population on the intestinal submucosa matrix to form a tissue graft; and

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injecting the cell-seeded tissue graft to a target tissue region in need of repair.

Upon implantation the cell populations assimilate into the tissue site, and promote vascularization at the implantation site.

Badyalak et al differs from the method of the instant claims in that they do not teach transiently transfecting either of the cell populations with a plasmid encoding an angiogenesis modulating agent, specifically VEGF.

Penn et al is relied upon for their disclosure that cell-based gene therapy, which involves transplantation of a cell type which has been transfected to express a therapeutic gene product, such as a growth factor, was an accepted technique in the art. Penn et al particularly disclose a method for augmenting cardiac function in ischemic myocardium by delivering myoblasts which have been transiently transfected with a plasmid encoding VEGF. Penn et al disclose the myoblasts assimilate into the cardiac tissue to restore function, and the VEGF increases vascular density, which is critical for restoring function in ischemic tissues.

Taken together, the references are held to render obvious a method wherein the transfected myoblasts of Penn et al are utilized as the 'at least one additional exogenous cell type' in the tissue graft of Badyalak et al, and the thus modified tissue graft is injected into ischemic myocardium to increase vascularization and restore cardiac function.

The combination of references still differs from current claim 33 in that neither Badyalak et al nor Penn et al teach or suggest encapsulating the transfected first cell population, and specifically do not teach encapsulation in alginate-PLL (poly(L-lysine)) microspheres (claims 36 and 37).

However, at the time the invention was made it was routine in the art to encapsulate cells so as to physically protect the transplanted cells from the recipients immune system, in this manner cells which

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secrete therapeutic agents, such as growth factors, hormones, etc, may be transplanted to a recipient to provide the therapeutic agent, but are protected from immune rejection (See Stewart et al, ¶0003-0006).

In the method of suggested by the art the transfected cell population is provided for the production of growth factor. As taught by Stewart et al, any transplanted cell may be subject to immune rejection, thus, in order to protect the genetically engineered cells to ensure that they survive to express the VEGF, it is submitted that it would have been *prima facie* obvious to one having ordinary skill in the art to encapsulate the genetically engineered first cell population, and provide this encapsulated first cell population along with the stromal tissue construct of Naughton et al to the target tissue site. Stewart et al disclose various microcapsules, including alginate-poly(L-lysine) microcapsules (please note microcapsules and microspheres are synonymous in this context) (See Stewart et al, ¶0010).

One would have had a reasonable expectation of successfully encapsulating the genetically engineered cell population in microspheres, such as alginate-poly(L-lysine) microspheres, because methods of such encapsulation were well known in the art, and are specifically disclosed by Stewart et al. Furthermore, Stewart et al disclose encapsulation of cells which have been genetically engineered to express VEGF (See Stewart et al, ¶0107).

Therefore, it is submitted that encapsulation of the 'first population of transfected cells', per the techniques disclosed by Stewart et al, in the method suggested by Badyalak et al and Penn et al would have been *prima facie* obvious to one skilled in the art in order to ensure immune privilege and physical protection for the genetically engineered cells of the tissue graft, so as to ensure the successful production of VEGF, which is beneficial in angiogenesis.

Therefore the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Claims 23, 25, 26 and 28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Naughton et al (US 2003/0007954), in view of Penn et al (US 2004/0161412 A1).

Naughton et al disclose a method for promoting blood vessel formation in tissues and organs by implanting a three-dimensional stromal tissue construct at a target site at or near the tissue or organ to promote endothelialization and angiogenesis in the tissue or organ. Naughton et al specifically disclose promoting blood vessel formation in the heart, including promoting vascularization and healing of ischemic myocardial tissue (See Naughton ¶ 0007-0008, 0028 & especially 0055-0057). The stromal tissue construct of Naughton et al is produced by:

(i) Providing a three-dimensional framework which allows cells to attach and grow in more than one layer. Materials suitable for the three-dimensional framework are disclosed at paragraphs 0032-0033 of Naughton et al, included in the listed materials are a number of polymers, such as nylon, Dacron, polystyrene, polypropylene, polyacrylates (¶0032), polyglycolic acid, collagen, and polylactic acid (¶0033). Collagen gel is also disclosed (¶0033); collagen gel is considered to read on a hydrogel.

(ii) Selecting a stromal cell population and inoculating said stromal cell population onto the three-dimensional framework. The stromal cells may be fibroblasts, or "specific" stromal tissue may be selected, such as stromal cells derived from the heart (See Naughton et al, ¶0034). Additional cell types may be seeded along with the fibroblasts/stromal cells, such additional cell types may include endothelial cells, skeletal muscle cells and cardiac muscle cells (See Naughton et al, ¶0038).

(iii) Culturing the stromal cell population with or without additional cell populations to form the three-dimensional stromal tissue construct (See Naughton et al, ¶0041-0045).

In a specific embodiment Naughton et al disclose preparing a genetically engineered three-dimensional stromal tissue by selecting stromal cells which are engineered to express an exogenous gene product (See Naughton et al, ¶0046-0048). The exogenous gene product secreted by the genetically engineered cells may enhance cell growth and/or promote angiogenesis; VEGF is specifically disclosed

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(See Naughton et al, ¶0049-0050). Cells that may be genetically engineered to express the exogenous gene product include the stromal cells, such as fibroblasts; Naughton et al also state additional cell types which can be genetically engineered include endothelial cells, smooth muscle cells, cardiac muscle cells, etc (See Naughton et al, ¶0048).

The stromal tissue construct of Naughton et al is then implanted at a target tissue site, such as adjacent to ischemic myocardium (See Naughton et al, ¶0055-0058). The stromal tissue construct may attach via natural adherence (i.e. the cells of the stromal tissue will assimilate into the existing tissue) and will promote formation of new blood vessels and healing within the target tissue (See Naughton et al, ¶0067-0068). Expression of the VEGF by the 'first cell population' will necessarily promote survival of both the stromal cells (second cell population) and the first cell population present within the tissue construct, as well as promote angiogenesis in the ischemic tissue.

The embodiment wherein the stromal cells and an additional cell population are co-cultured together on the three-dimensional framework, and wherein the 'additional cell population' comprises genetically engineered cells, is being relied upon for this rejection; the method of Naughton et al is comparable to the method of the instant claims as follows:

The three-dimensional framework is considered to read on a matrix material as defined by the instant claims. The three-dimensional framework may be comprised of a polymeric material, such as a woven mesh of PGA, PLA, collagen (relevant to claim 26), or of a collagen gel (relevant to claim 25).

The stromal cells are considered to read the second cell population, as defined by the claims, and the additional cells are considered to read on the first cell population, as defined by the claims.

The step of genetically engineering the additional cell type (the 'first population of cells') to express VEGF is comparable to the claimed step of "transiently transfecting a first population of cells

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with a plasmid encoding an angiogenesis modulating agent." VEGF as the angiogenesis modulating agent is relevant to claim 28.

The step of actively culturing the stromal cell population (the 'second population of cells') and the genetically engineered additional cell population (the 'transfected first population of cells') on the three-dimensional framework is considered to read on the claimed step of "culturing at least a second population of cells on a matrix material to produce an organ construct."

Finally, the step of implanting the stromal tissue comprising the stromal cells (the 'second cell population') and the genetically engineered additional cell population (the 'transfected first cell population') adjacent to ischemic myocardial tissue is considered to read on the claimed step of "implanting the organ construct and the first population of cells *in vivo* at a target site to replace or augment organ function, such that the first population of cells express the angiogenesis modulating agent." Expression of the VEGF by the 'first cell population' will necessarily promote survival of both the stromal cells (second cell population) and the first cell population present within the tissue construct, as well as promote angiogenesis in the ischemic tissue, thus the method of Naughton et al is considered to effectively "induce the second population of cells to assimilate and differentiate at the target site."

The method of Naughton et al differs from the instant claims with regards to the step of *transiently* transfecting the first population of cells *with a plasmid* encoding an angiogenesis modulating agent. Naughton et al uses viral transfection methods to insert the desired gene sequence into the cell DNA under control of a promoter (See Naughton et al, ¶0052-0054); Naughton et al further does not teach transient transfection.

However, at the time the invention was made Penn et al taught a method for transiently transfecting a population of skeletal myoblasts with a VEGF expression vector by plasmid DNA transfection (See Penn et al, ¶0092 & ¶0100-0102).

Because both Naughton et al and Penn et al disclose methods for successfully genetically engineering cells to express a target gene product (specifically VEGF), it would have been obvious to one skilled in the art to substitute one method (plasmid DNA transfection, as taught by Penn et al) for the other (viral transfection, as taught by Naughton) to achieve the predictable result of transfecting the cell so that it expresses the target gene produce (VEGF). Substitution of one method step for another known in the field is considered to be obvious, absent a showing that the result of the substitution yields more than predictable results. See *KSR International Co. v Teleflex Inc* 82 USPQ2d 1385 (US 2007) at page 1395.

Furthermore, Penn et al state that the myoblasts cells which transiently express VEGF are useful to stimulate cell differentiation and regenerate ischemia damaged tissue (See Penn et al, ¶0020 & ¶0044-0045). Penn et al teach that local and transient expression of VEGF is sufficient to induce neovascularization, while minimizing systemic effects and hemangioma formation (See Penn et al, ¶0004).

Because local and transient expression of the VEGF in ischemic myocardial tissue can achieve the same benefits of stimulating cell differentiation and tissue regeneration without the negative consequences of constitutive expression of VEGF (hemangioma formation) it is submitted that one would have been motivated to transiently transfect the cells by the method of Penn et al. One would have had a reasonable expectation of successfully transiently transfecting the additional cell population (the endothelial and/or cardiac muscle cells) of Naughton et al by the techniques of Penn et al based on the success shown by and detailed protocols provided by Penn et al in their disclosure.

Thus it is submitted that it would have been *prima facie* obvious to one having ordinary skill in the art to modify the method of Naughton et al so as to transiently transfecting the 'first cell population' with a plasmid encoding VEGF so that the cells transiently express the VEGF; with this modification, the method of Naughton et al reads on the method of instant claims 23, 26 and 28.

Therefore the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Claims 23, 25, 26, 28, 40 and 41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Naughton et al (US 2003/0007954), in view of Penn et al (US 2004/0161412 A1).

The teachings of Naughton et al and Penn et al are set forth in detail above. Briefly, Naughton et al disclose a method for augmenting organ function, specifically improving cardiac function of ischemic myocardial tissue, comprising:

- transfecting a first population of cells to express angiogenesis modulating agent VEGF;
- co-culturing the transfected first population of cells with a second population of stromal cells on a three-dimensional matrix to form an organ construct; and
- implanting the organ construct adjacent to ischemic myocardial tissue.

Upon implantation both cell populations assimilate into the tissue site, thereby improving cardiac function and promoting angiogenesis. The transfected first population of cells will necessarily express the VEGF, which will aid in survival of the cells of the transplanted organ construct, as well as improve angiogenesis at the target tissue site.

Naughton et al differs from the method of the instant claims in that they do not teach transiently transfecting the first cell population with a plasmid encoding VEGF. However, it has been shown that it would have been *prima facie* obvious to modify the method of Naughton et al to utilize transient transfection by plasmid based on the teachings of Penn et al, who teach that transient transfection of VEGF is desirable in treatment of ischemic myocardium because it is sufficient to induce angiogenesis, but does not cause hemangioma formation.

The method of Naughton et al differs from current claims 40 and 41 in that Naughton et al does not disclose vascular endothelial cells (claim 40) or myoblasts (claim 41) as the additional cell population (the 'first cell population') which may be genetically engineered to express VEGF.

However, Naughton et al defines the additional cell population using non-limiting language (See Naughton et al, ¶0038). Naughton et al does disclose endothelial cells (generically) and both skeletal and cardiac muscle cells (Naughton et al, ¶0038).

With regards to vascular endothelial cells, it is first reiterated that Naughton et al does suggest endothelial cells (generically), it is submitted that it would have been *prima facie* obvious to one of ordinary skill in the art to utilize *vascular* endothelial cells within the organ construct because Naughton et al intends to promote formation of blood vessels at the target tissue site. Vascular endothelial cells present within the organ construct could readily participate in development of new blood vessels as part of angiogenesis, as blood vessels comprise vascular endothelial cells. One would have had a reasonable expectation of successfully employing vascular endothelial cells as the "transiently transfected first cell population" which may be employed in the method of Naughton et al because Penn et al disclose a process for transiently transfecting cells using a plasmid DNA transfection (See Penn et al, ¶0092); the same transfection method may be applied to any cell type (See Penn et al, ¶0069).

With regards to myoblasts, it is reiterated that Naughton et al does suggest both skeletal and cardiac muscle tissue; myoblasts are muscle progenitor cells. Furthermore, it is submitted that Penn et al specifically disclose myoblasts as a desirable cell type for implantation at a site of ischemic myocardium for augmentation of cardiac function (See Penn et al, ¶0020 & ¶0044-0045); therefore myoblasts were recognized in the art as being utility in treating myocardial ischemia. One would have had a reasonable expectation of successfully employing myoblasts as the "transiently transfected first cell population" which may be employed in the method of Naughton et al because Penn et al specifically exemplify transient transfection of myoblasts to transiently express VEGF.

Therefore the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Claims 23-26 and 28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Naughton et al (US 2003/0007954), in view of Penn et al (US 2004/0161412 A1), and further in view of Atala (US Patent 6,479,064).

The teachings of Naughton et al and Penn et al are set forth in detail above. Briefly, Naughton et al disclose a method for augmenting organ function, specifically improving cardiac function of ischemic myocardial tissue, comprising:

transfecting a first population of cells to express angiogenesis modulating agent VEGF;
co-culturing the transfected first population of cells with a second population of stromal cells on a three-dimensional matrix to form an organ construct; and
implanting the organ construct adjacent to ischemic myocardial tissue.

Upon implantation both cell populations assimilate into the tissue site, thereby improving cardiac function and promoting angiogenesis. The transfected first population of cells will necessarily express the VEGF, which will aid in survival of the cells of the transplanted organ construct, as well as improve angiogenesis at the target tissue site.

Naughton et al differs from the method of the instant claims in that they do not teach transiently transfecting the first cell population with a plasmid encoding VEGF. However, it has been shown that it would have been *prima facie* obvious to modify the method of Naughton et al to utilize transient transfection by plasmid based on the teachings of Penn et al, who teach that transient transfection of VEGF is desirable in treatment of ischemic myocardium because it is sufficient to induce angiogenesis, but does not

The combination of references still differs from current claim 24 in that Naughton et al does not disclose use of a decellularized tissue as the three-dimensional scaffold material for formation of the stromal tissue construct.

However, it is submitted that Naughton et al use open language to define the material of the three-dimensional framework which may be used as the matrix material, Naughton et al state the only requirements for the matrix material are that it must be (a) allow cells to attach to it (or can be modified to allow cells to attach to it); and (b) allows cells to grow in more than one layer (See Naughton et al, ¶0031).

At the time the invention was made the art taught numerous matrix materials which satisfied the requirements of Naughton et al for use as the three-dimensional framework material, including decellularized tissue. Specifically, Atala discloses decellularized tissues as suitable matrix material for formation of an artificial organ (See, Atala, ¶ 0012). Matrices used by Atala allow cells to attach and to develop into neomorphic organ augmenting units, which would be understood to comprise cells growing in more than one layer (See Atala, ¶0009-0011).

Therefore, because Naughton et al and Atala both disclose scaffold materials which are capable of supporting cell attachment and growth in more than one layer, it would have been *prima facie* obvious to one of ordinary skill in the art to substitute one matrix material (the decellularized tissue of Atala) for the other (the disclosed materials of Naughton et al) for the predictable result of successfully supporting growth of cells thereupon for formation of an engineered tissue construct which may subsequently be implanted at a target site. Substitution of one element for another known in the field is considered to be obvious, absent a showing that the result of the substitution yields more than predictable results. See *KSR International Co. v Teleflex Inc* 82 USPQ2d 1385 (US 2007) at page 1395.

Therefore the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Claims 23, 25, 26, 28, 33, 36 and 37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Naughton et al (US 2003/0007954), in view of Penn et al (US 2004/0161412 A1), and further in view of Stewart et al (US 2006/0251630).

The teachings of Naughton et al and Penn et al are set forth in detail above. Briefly, Naughton et al disclose a method for augmenting organ function, specifically improving cardiac function of ischemic myocardial tissue, comprising:

transfecting a first population of cells to express angiogenesis modulating agent VEGF;
co-culturing the transfected first population of cells with a second population of stromal cells on a three-dimensional matrix to form an organ construct; and
implanting the organ construct adjacent to ischemic myocardial tissue.

Upon implantation both cell populations assimilate into the tissue site, thereby improving cardiac function and promoting angiogenesis. The transfected first population of cells will necessarily express the VEGF, which will aid in survival of the cells of the transplanted organ construct, as well as improve angiogenesis at the target tissue site.

Naughton et al differs from the method of the instant claims in that they do not teach transiently transfecting the first cell population with a plasmid encoding VEGF. However, it has been shown that it would have been *prima facie* obvious to modify the method of Naughton et al to utilize transient transfection by plasmid based on the teachings of Penn et al, who teach that transient transfection of VEGF is desirable in treatment of ischemic myocardium because it is sufficient to induce angiogenesis, but does not

The combination of references still differs from current claims 33 in that neither Naughton et al nor Penn et al teach or suggest encapsulating the transfected first cell population, and specifically do not teach encapsulation in alginate-PLL (poly(L-lysine)) microspheres (claims 36 and 37).

However, at the time the invention was made it was routine in the art to encapsulate cells so as to physically protect the transplanted cells from the recipients immune system, in this manner cells which secrete therapeutic agents, such as growth factors, hormones, etc, may be transplanted to a recipient to provide the therapeutic agent, but are protected from immune rejection (See Stewart et al, ¶0003-0006).

In the method of Naughton et al the additional cell population (i.e. the first cell population) may be provided for their production of growth factor, genetic engineering of this additional cell population enhances the production of the desired growth factor. As taught by Stewart et al, any transplanted cell may be subject to immune rejection, thus, in order to protect the genetically engineered cells to ensure that they survive to express the VEGF, it is submitted that it would have been *prima facie* obvious to one having ordinary skill in the art to encapsulate the genetically engineered first cell population, and provide this encapsulated first cell population along with the stromal tissue construct of Naughton et al to the target tissue site. Stewart et al disclose various microcapsules, including alginate-poly(L-lysine) microcapsules (please note microcapsules and microspheres are synonymous in this context) (See Stewart et al, ¶0010).

One would have had a reasonable expectation of successfully encapsulating the genetically engineered additional cell population of Naughton et al (the 'first cell population') in microspheres, such as alginate-poly(L-lysine) microspheres, because methods of such encapsulation were well known in the art, and are specifically disclosed by Stewart et al. Furthermore, Stewart et al disclose encapsulation of cells which have been genetically engineered to express VEGF (See Stewart et al, ¶0107).

Therefore, it is submitted that encapsulation of the 'first population of transfected cells', per the techniques disclosed by Stewart et al, in the method of Naughton et al would have been *prima facie*

obvious to one skilled in the art in order to ensure immune privilege and physical protection for the genetically engineered cells of the stromal tissue, so as to ensure the successful production of VEGF, which is beneficial in angiogenesis.

Therefore the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ALLISON M. FORD whose telephone number is (571)272-2936. The examiner can normally be reached on 8:00-6 M-Th.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn can be reached on 571-272-0926. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Art Unit: 1651

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Allison M. Ford/
Primary Examiner, Art Unit 1651